REMARKS

Claim Rejections- 35 USC § 112 para. 2

Applicant submits that the currently amended claims are fully responsive to the Examiner's rejections.

Briefly, as described in the amended claims, the liposomal formulation of the present invention consists substantially of phospholipids and a therapeutically effective amount of a non-polar di- or tetrahydro porphyrin derivative selected from chlorin, bacteriochlorin, porphyrinogen, or iso bacteriochlorin. An inventive formulation, as now claimed in amended claim 3, contains at least one poly (ethylene glycol) linked phospholipid (a "Pegylated phospholipid") and one or more monosaccharides or polyalcohols.

In particular, claims 1, 3, and 5 have been amended and claim 4 has been cancelled. Applicant respectfully requests that Examiner's 35 USC s. 112 para. 2 rejection be withdrawn as it no longer applies.

Claim Rejections – 35 USC § 102

1. Claims 1-4, 11 and 13 were rejected as being anticipated by Desai et al. in US 6,074,666 ('666).

To anticipate the present invention, '666 must teach each and every element as set forth in the claims. MPEP 2131. However, a close reading of '666 will confirm that the reference does not meet the "every element" requirement and thus does not anticipate the present invention.

Desai *et al.* disclose a liposomal formulation comprising a porphyrin photosensitizer derivative, a disaccharide or polysaccharide and one or more phospholipids ('666, Col. 3, lines 35- 40). Photosensitizers that were specifically disclosed as being particularly suited for use in the '666 invention were deuteroporphyrin, etioporphyrin, protoporphyrin, hematoporphyrin, pheophorbide and derivatives thereof ('666, Col. 3, lines 46-52). In addition, '666 teaches that the combination of a

disaccharide or polysaccharide and one or more phospholipids is necessary for retaining a small particle size when reconstituting the reference liposomes ('666, Col. 5, lines 23-30) and specifically teaches that no more than 4-5% monosaccharides can be added to the disclosed liposome formulation ('666, Col. 5, lines 45-50). However, '666 neither expressly nor implicitly discloses or suggests a formulation that incorporates at least one Pegylated phospholipid and one or more monosaccharides or does not require any saccharides.

To contrast, the liposome formulation of the present invention contains one or more monosaccharides and at least one Pegylated phospholipid. Including at least one Pegylated phospholipid in the present liposome formulation is critical to achieving the drug delivery objectives of the present invention, namely, improved transport through cell membranes, selective targeting, and increased resistance to degradation *in vivo*.

Because '666 does not teach or suggest the use of phospholipids having a poly (ethylene glycol) linkage ("Pegylated phospholipids") and one or more monosaccharides, or the use of monosaccharides, '666 fails to disclose each and every element of the present invention. Accordingly the present invention is not anticipated by '666.

2. Claims 1-3 and 5-12 were rejected as being anticipated by Madden in US 5,389,378 ('378).

To anticipate the present invention, '378 must teach each and every element as set forth in the claims. MPEP 2131. However, as discussed below, this reference does not meet the "every element" requirement and therefore does not anticipate the present invention. Moreover, the Examiner has not presented a factual basis or objective technical evidence to support a theory of inherency. See MPEP 2112.

Madden discloses liposome formulations containing mono- and di-acid benzoporphyrin derivatives (BPD) with a high drug to lipid ratio. The reference liposomes optionally include a steroidal component selected from the group cholesterol, cholestanol, coprostanol or cholestane or polyethylene glycol derivatives of cholesterol (PEG-cholesterols). ('378, Col. 8, lines 27-48) The reference also teaches that one or

more sugars are needed when dehydrating the disclosed BPD-containing liposomes, however, expressly state that "disaccharide sugars work better than monosaccharides." ('378, Col. 9, lines 8-15) In contrast to the present invention, '378 neither teaches nor suggests the use of Pegylated phospholipids. Instead, '378 specifically teaches that the disclosed PEG-derivatives (e.g. PEG-cholesterol) "may be used alone or preferably in combination with any of the above-mentioned phospholipids." ('378, Col. 8, lines 43- 48) In effect, the teachings of '378 implicitly excludes the use of Pegylated phospholipids.

Moreover, the Examiner has not presented a factual basis and/or technical reasoning to support that use of at least one Pegylated phospholipid and one or more monosaccharides are inherent in and necessarily flow from the teachings of '378. See MPEP 2112. To establish inherency, it is not enough that "a certain result or characteristic may occur or be present" in the reference. Instead, it is incumbent on the Examiner to provide objective evidence and/or cogent technical reasoning to support the conclusion of inherency.

Thus, because the teachings of '378 do not suggest or include the use of Pegylated phospholipids, '378 fails to meet the "every element" requirement and therefore does not anticipate the present invention. Further, the present invention is not anticipated by '378 because no basis for inherency has been shown.

3. Claims 1, 3-4, 11-12, and 15 were rejected as being anticipated by GB 2,146,525 ('525).

Similarly, '525 must teach each and every element as set forth in the claims to anticipate the present invention. As discussed below,'525 does not meet the "every element" requirement and therefore does not anticipate the present invention.

GB '525 discloses a liposomal drug delivery system that targets and delivers drugs to tumor sites as a consequence of having porphyrins bound to the outermost layer of the liposomes. ('525, p. 2, lines 50-56) Five specific porphyrin species were identified as being suitable targeting ligands for the reference invention: hematoporphyrin IX (HP), Hematoporphyrin IX derivative (HPD), deuteroporphyrin IX (DP), Mesoporphyrin IX

(MP), and protoporphyrin IX (PP). ('525, p. 2, lines 10-15) The targeted drug delivery system of the reference also includes an encapsulated drug which may be incorporated into the inner aqueous region and/or the lipid region of the liposome depending on its solubility. ('525, p. 2, lines 1-8)

In direct contrast to the present invention, '525 teaches a means for turning the liposome "into a system which has the ability to target itself in vivo from the site of administration to the site of drug action." This "targeting ability is conferred upon the [reference] liposome by a porphyrin [that is] bound covalently or non-covalently to the outermost membrane of the pre-formed liposome." ('525, p. 2, lines 13-15) Moreover, '525 does not disclose, teach, or suggest the use of polyethylene glycol linked liposomes (Pegylated liposomes) or Pegylated phospholipids.

As already discussed, Applicants' liposome formulation contains one or more monosaccharides and at least one Pegylated phospholipid. Including at least one Pegylated phospholipid in the present formulation is critical to achieving the drug delivery objectives of the present invention, namely improved cellular transport, increased resistance to *in vivo* degradation, and selective targeting. Because '525 does not suggest or teach the use of Pegylated liposomes or Pegylated phospholipids, '525 fails to meet the "every element" requirement and fails to anticipate the present invention.

Claim Rejections – 35 USC § 103

As recited in MPEP 2143 *et seq.*, to establish a *prima facie* case of obviousness, three basic criteria must be met:

(1) There must be some suggestion or motivation to modify the teachings of the reference.

(2) There must be a reasonable expectation of success.

(3) The references must teach or suggest all the claim limitations.

1. Claims 5-10, 12 and 14 were rejected as being unpatentable over Desai *et al.* ('666) in view of Madden ('378).

The *prima facie* case of obviousness has not been established with respect to '666 in view of '378 because the references do not disclose all of the elements of the present invention as set out in the claims nor do the references suggest, teach, or imply a motivation to combine the reference teachings in order to produce the present invention. Furthermore, despite '378 teaching the use of a variety of sugars, including monosaccharides, both cited references reject the use of monosaccharides in porphyrin-derivative liposome formulations. Instead, both references indicate that certain desirable characteristics either would be hindered or precluded with the use of monosaccharides in a porphyrin-liposome formulation. As a result, neither of the cited references, nor the combination of the two, create a reasonable expectation of success regarding the use of monosaccharides in a porphyrin-derivative liposome formulation. For these reasons, Applicants respectfully submit that the present invention is patentable over the cited references.

In rejecting the use of monosaccharides in porphyrin-liposome formulations, '378 states that "disaccharides sugars work better than monosaccharides," while '666 teaches that "disaccharides or polysaccharides are preferred to monosaccharides" because the higher sugars enhance the reproducibility and range of particle sizes of the reference liposomes. ('666, Col. 5, lines 45-46 and 23-26) The '666 formulations, which contained 8-12% of either lactose or trehalose, were disclosed as having a mean particle size of "less than 200 nm." ('666, Col. 11, lines 1-5) However, to keep the osmotic pressure of the liposome formulation similar to blood, '666 teaches that no more than 4-5% monosaccharide can be present. ('666, Col. 5, lines 45-48) Finally, as already discussed, neither reference disclosed or suggested the use of Pegylated phospholipids in combination with one or more monosaccharides.

Contrary to the reference teachings, Applicants' formulation may contain between 2-12% monosaccharide, as shown in example 1c on page 8 of the present application. Moreover, in direct contrast to the teachings of '666, Applicants' formulations also had a mean particle size below 200 nm, namely, 166 nm, and were found to function well. (Present application, page 8)

Clearly, both references advocate against the use of monosaccharides in order to achieve and maintain a storage-stable liposome with a reproducible and desirable particle size. Accordingly, the reference teachings do not create a reasonable expectation of success that a formulation having a particle size less than 200 nm would result from a liposome having at least one Pegylated phospholipid and one or more monosaccharides or polyalcohols. Moreover, the combination of these two references do not encompass each and every element of the present invention. For these reasons, the present invention is patentable over Desai *et al.* in view of Madden.

2. Claims 15 and 16 were rejected as being unpatentable over Desai *et al.* ('666) in view of GB 2,146,525 ('525).

As discussed above, the cited references, alone or in combination, fail to disclose, teach, or imply all of the elements of the present invention as set forth in the amended claims. Accordingly, the present invention is patentable over '666 in view of '525 because neither reference discloses or suggests the use or desirability of a Pegylated liposome formulation or a liposome formulation comprised of at least one Pegylated phospholipid and one or more monosaccharides for intravenous injection.

3. Claims 2, 5-10, 12-14, and 16 were rejected as being unpatentable over GB 2,146,525 in view of '378.

As discussed above, the cited references, alone or in combination, fail to disclose, teach, or imply all of the elements of the present invention as set forth in the amended claims. As such, the present invention is patentable over '525 in view of '378 because neither reference discloses or suggests the desirability of a liposomal formulation comprised of at least one Pegylated phospholipid and one or more monosaccharides or polyalcohols. Moreover, the references do not suggest combining or modifying the teachings so as to produce the present invention as claimed. Finally, there is no expectation of success created by the teachings of '525 in view of '378.

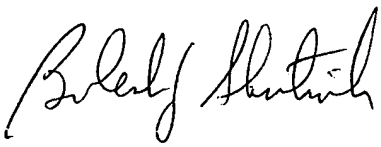
Despite the disclosure of liposomal formulations containing various porphyrins, '525 teaches directly away from '378 and the present invention by using the porphyrin as a targeting ligand as opposed to an anti-tumor agent. Indeed, as discussed in '525 on page 6, the stability of the reference formulation is evaluated by observing the retention of the porphyrin within the liposomal membrane over time. To contrast, '378 and the present invention primarily rely on the release of the porphyrin photosensitizers from the liposome to achieve tumor eradication via light-activated cytotoxicity.

Further, because '378 does not teach or suggest a formulation where porphyrins are bound (e.g. attached to the outermost surface) to the liposome, '378 provides no teachings regarding the effects that dehydrating/lyophilizing with have on a porphyrin-bound liposome formulation of the type disclosed in '525. As a result, no expectation of success is created by the teachings of '525 in view of '378 regarding the presence and effect of protective sugars on the stability of a porphyrin-derivative liposome formulation comprised of at least one Pegylated phospholipid.

In failing to satisfy the three basis criteria of obviousness, the present invention is patentable over '525 in view of '378.

With these changes and remarks, it is believed that the disclosure is now in condition for allowance and reconsideration is respectfully requested. An early and favorable response is earnestly solicited. Thank you.

Respectfully submitted,



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